UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,774	07/13/2006	Mehmet Toner	022727-0138	3248

21125 7590 12/03/2007

NUTTER MCCLENNEN & FISH LLP
WORLD TRADE CENTER WEST
155 SEAPORT BOULEVARD
BOSTON, MA 02210-2604

EXAMINER	
KOSSON, ROSANNE	
ART UNIT	**PAPER NUMBER**
1652	

NOTIFICATION DATE	DELIVERY MODE
12/03/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@nutter.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,774	TONER ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *3,4,7,18,24,25,31,36,42 and 46-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8-17,19-23,26-30,32-35,37-41 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election without traverse of Group I, a method for preserving a biomaterial/mammalian cell in which the transporter protein is a glucose transporter protein, claims 1-45 to the extent that these claims read on the elected invention, in the reply filed on October 24, 2007 is acknowledged. Applicants' elections of the species of freezing as the preservation method, frozen state as the storage method, cell as the biomaterial and 3-O-methyl-glucose (OMG) as the non-metabolizable carbohydrate are also acknowledged. Claims 3, 4, 7, 18, 24, 25, 31, 36, 42 and 46-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions, there being no allowable generic or linking claim. No claims have been amended, canceled or added. Accordingly, claims 1, 2, 5, 6, 8-17, 19-23, 26-30, 32-35, 37-41 and 43-45 are examined on the merits herewith to the extent that they read on the elected invention.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 6, 8-17, 19-23, 26-30, 32-35, 37-41 and 43-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite a

method of preserving a biomaterial having a membrane and a transporter molecule or transporter protein in which the biomaterial is exposed to a preservation agent. Some of the instant claims recite the invention more narrowly, as a mammalian cell instead of a biomaterial, or in which the preservation agent is a non-metabolizable carbohydrate. But, even the claims that recite a method of preserving a mammalian cell also recite that the genus of any transporter protein may be used in the method. Thus, the claims recite three vast genera for each of which only a very few species are disclosed. The genus of a biomaterial having a membrane reads on things as different as whole animals, whole plants, packaged foods, medical supplies, packaged cosmetics, pharmaceuticals and nutraceuticals, etc. But, the specification makes it clear that the biomaterial having a membrane is a mammalian cell. The genus of a transporter molecule includes any type of molecule as well as all proteins- e.g., lipids, polysaccharides, polynucleotides, organic molecules. In the specification, however, the only transporter molecules or transporter proteins disclosed are the trans-membrane GLUT transporter proteins for monosaccharides and disaccharides. The genus of a preservation agent reads on any preservative, e.g., an antibiotic, insecticide, antioxidant, nitrite, sulphite, EDTA or formaldehyde. The only preservative agents disclosed in the specification are glucose and several non-metabolizable glucose analogues, sucrose, mannose, galactose and a hexose. A sufficient written description of a genus of cells, proteins or preservation agents (monosaccharides or disaccharides) may be achieved by a recitation of structural features common to each member (species) of the genus, **which features constitute a substantial portion of each member of the genus**. The only recited structural feature of the genus of biomaterial in these claims (i.e., any biocompatible material having any kind of membrane) does not constitute a substantial portion of each species in the genus, as the remainder of the structure is completely undefined and the specification does not define the remaining structural features necessary for members

of the genus to be selected. The structural features needed for the transporter molecule or protein to function in transporting the monosaccharide or disaccharide across a cell membrane also are not recited. As noted above, the specification makes it clear that, for a preservation agent to function in the claimed method it must be structurally a mono- or disaccharide. Therefore, one skilled in the art cannot reasonably conclude that Applicants had possession of the claimed invention at the time the instant application was filed.

Consequently, there is no evidence that a sufficient number of representative species of these very large genera were in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Because only a very limited number of species of each of the claimed genera are disclosed, the claims fail to satisfy the written description requirement.

Claims 1, 2, 5, 6, 8-17, 19-23, 26-30, 32-35, 37-41 and 43-45 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the genera of: 1) a mammalian cell as the biomaterial having a membrane that is preserved by the claimed method, 2) a glucose transporter protein or GLUT protein as the transporter protein or transporter molecule, and 3) glucose, a non-metabolizable glucose analogue, a hexose, sucrose, mannose or galactose as the preservation agent, does not reasonably provide enablement for the genera in the claimed method of any biomaterial having a membrane, any transporter molecule/protein and any preservation agent. As a result, the specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue

experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

1.Breadth of the claims.

The claims are very broad because they recite a method of preserving any biomaterial having a membrane and a transporter molecule by exposing it to a preservation agent.

2. The nature of the invention.

The invention is designed to provide a novel method for preserving a mammalian cell.

3. The state of prior art.

See the discussion of Toner et al. (US 6,127,177), Gould et al. ("The glucose transporter family: structure, function and tissue-specific expression," Biochem J 295:329-341, 1993), and Pescero et al. ("Glucose metabolism by trout (*Salmo trutta*) red blood cells," J Comp Physiol B 162:448-454, 1992 below. Curtis (US 2003/0009024 A1) was discussed in the previous Office action.

4. The relative skill in the art.

The relative skill in the art as it relates to the method of the invention is characterized by that of a M.D. or Ph. D. level individual.

5. The level of predictability in the art.

Because the effect of exposing any biomaterial having a membrane and a transporter

molecule to a preservation agent is not known, particularly because each term is so broad that it encompasses a vast set of highly different and unrelated things, the specification needs to have more detail so that the properties of each combination of these three things will be predictable and so that one of skill in the art would know which three specific, concrete things to use together so that the claimed method will work. Because the prior art and the instant specification disclose that the biomaterial is a mammalian cell, the transporter molecule is a GLUT protein and the preservation agent is glucose, a non-metabolizable glucose analogue or one of several disaccharides, it cannot be predicted that any membrane-containing biomaterial, any transporter molecule and any preservation agent would retain the structural and functional properties of the specifically disclosed species so that the claimed method will work.

6. The amount of guidance present.

As noted above, Applicants have provided guidance only for the biomaterial of a mammalian cell, the transporter molecule of a GLUT protein (the specific GLUT protein is not indicated) and the preservation agent of glucose, a non-metabolizable glucose analogue or one of several disaccharides.

7. The existence of working examples.

The limited guidance mentioned above is presented in working examples.

8. The quantity of experimentation necessary.

To prove that any biomaterial having a membrane, any transporter molecule or protein and any preservation agent may be used in the claimed method, many experiments would have to be conducted under a wide range of conditions in order to determine which species from each genus may be used together. In these experiments, many membrane-containing biomaterials would have to be studied to determine which transporter molecules they contain. A preservation agent would have to be identified for each transporter molecule. The biomaterial

would have to be tested under many different physical conditions (ranges of temperature, pH, dryness, oxygen content, immersion in different solutions, etc.) to determine under which conditions the transporter molecule can transport the preservation agent into the biomaterial.

These types of experiments and data are missing from the specification. A great deal of experimentation is needed to establish that any membrane-containing biomaterial, any transporter molecule and any preservation agent may be used in the claimed method, because these genera are claimed, while very few species of each genus are disclosed. Even if one combination of biomaterial, transporter molecule and preservation agent could be made and identified, by random, trial-and-error construction and testing, without a very large amount of data, such a result could not be expected with a different biomaterial, transporter molecule and preservation agent, particularly when tested in a different assay, or under different assay conditions, than the first combination of components.

In view of the foregoing, the claims fail to satisfy the enablement requirement.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim recites the limitation "non-metabolizable preservation agent." There is insufficient antecedent basis for this limitation in the claim. Appropriate correction is required. The term may be amended to "preservation agent," as recited in claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 6 and 8-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Toner et al. (US 6,127,177), as evidenced by Gould et al. ("The glucose transporter family: structure, function and tissue-specific expression," Biochem J 295:329-341, 1993).

Toner et al. disclose a method for preserving mammalian cells, such as fibroblasts, hepatocytes, bone marrow cells and granulocytes, comprising the steps of exposing them to a solution of a preservation agent, a mono- or disaccharide, such as glucose, freezing them, and storing them in the frozen state (see cols. 1 and 2; col. 4, lines 10-55; and Fig. 1). At least a portion of these frozen cells may be recovered in a viable state (see Fig. 1; col. 5, lines 10-23 and 46-67; col. 8, lines 51-64; and cols. 12-14). The preservation agent is removed from the cells by thawing the frozen cells, incubating them in fresh cell culture medium- DMEM- which reverses the poration of the cell membrane, and washing the cells and resuspending them in additional volumes of cell culture medium, which further dilutes the preservation agent (see col. 5, lines 62-67; and col. 6, lines 47-64).

Gould et al. disclose that mammalian cells naturally possess a variety of glucose transporter proteins (GLUT's), at least seven different types, and that the type of GLUT depends on the type of tissue (see pp. 329-330). Thus, in the method of Toner et al., the transporter molecule or transporter protein is part of and is present in the mammalian cells and is able to import sugars such as glucose.

In view of the foregoing, a holding of anticipation is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 6, 8-17, 19-23, 26-30, 32-35, 37-41 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toner et al. (US 6,127,177) in view of Gould et al. ("The glucose transporter family: structure, function and tissue-specific expression," Biochem J 295:329-341, 1993); and Pescero et al. ("Glucose metabolism by trout (*Salmo trutta*) red blood cells," J Comp Physiol B 162:448-454, 1992.

The teachings of Toner et al. and Gould et al. are discussed above. Toner et al. do not disclose using a non-metabolizable carbohydrate as the preservation agent.

Pescero et al. disclose that 3-O-methyl-glucose (OMG) is a non-metabolizable carbohydrate and glucose analogue that is taken up by mammalian cells through their cell membranes. Glucose, a fuel source, is the most widely used monosaccharide in vertebrate cells, and vertebrates have a higher plasma concentration of glucose than of other monosaccharides. Glucose is metabolized in the glycolytic cycle to generate carbon dioxide,

ATP and lactic acid (see p. 448). More acid, lactic acid, is produced from glucose than from other glycolytic intermediates, even under aerobic conditions (see p. 450, left col.). Because OMG is not metabolized, it is detectable in experiments even after 1000 min. (see p. 449, Fig. 1). Thus, there is no acid production from OMG.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a non-metabolizable glucose analogue, such as OMG, in the method of Toner et al., because Pescero et al. disclose that glucose, although readily taken up by cells, is also readily metabolized to lactic acid in the glycolytic cycle. One of ordinary skill in the art would have known that the glycolytic cycle produces other acid intermediates as well, such as pyruvic acid. Pescero et al. disclose that OMG, which is not metabolized, does not produce acid. One of ordinary skill in the art would have recognized the advantage of using a preservation agent that is stable and that does not drop the pH of the culture medium (by causing acid production), because he would have known that the preserved cell culture would have lasted longer and that the cells would have been in better health, by being in a medium at a more desirable pH.

Regarding the concentration of the preservation agent, Toner et al. disclose that the concentration in their method is a low level, less than or equal to 1 M (see col. 1, lines 66-67). Toner et al. also disclose concentrations of 0.2 M and 0.4 M (see col. 9, lines 47-56; and col. 11, lines 28-43). Thus, it would have been obvious one of ordinary skill in the art at the time of the invention to use 0.2-1 M of OMG in the method of Toner et al., as Toner et al. disclose that these concentrations of sugar are effective for cell preservation. One of ordinary skill in the art would have expected these concentrations of OMG to have been effective for cell preservation.

In view of the foregoing, a holding of obviousness is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

rk/2007-11-05

Rosanne Kosson

REBECCA S. PROUTY
PRIMARY EXAMINER
GROUP 1600